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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
683-114PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/01347	20/11/2000	18/11/1999
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant GENESENSE TECHNOLOGIES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/05/2001	27.03.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mundel, C Telephone No. +49 89 2399 7314

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/01347

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-66 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/38-38/38 as originally filed

Sequence listing part of the description, pages:

2-117, filed with the letter of 27.02.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-40 (partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-40 (partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-40 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 15-26, 29, 31, 34-35 and 38-39
	No:	Claims	1-2, 4-14, 27-28, 30, 32-33, 36-37 and 40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40 (NO)
Industrial applicability (IA)	Yes:	Claims	1-39
	No:	Claims	40 (see Citations and explanations)

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The International Search Authority identified a unity problem in the present application. Since the applicant didn't pay any additional fees, claims 1-40 have only be searched as far as they refer to SEQ ID NO: 16.

Re Item IV

Lack of unity of invention

According to **Rule 13 PCT** an application must relate only to one invention or to a group of inventions so linked as to form a **single inventive concept**, i.e. having at least one common technical feature defining a contribution over the known prior art.

The IPEA agrees with the ISA advices that the present application lacks unity and identifies the following groups of inventions in the international application :

1. Claims : 1-40 (partially)

   An antisense compound 5 to 50 nucleobases in length targeted to a nucleic acid molecule encoding groEL or groES of a microorganism specifically hybridizing with and inhibiting the expression of groEL or groES, a composition comprising said antisense compound and a pharmaceutically acceptable carrier or diluent, a method of inhibiting the expression of groEL or groES in cells or tissues in vitro comprising contacting said cells or tissues with said antisense compound, an antisense compound up to 50 nucleobases in length targeted to a nucleic molecule encoding groEL or groES comprising at least a 5 nucleobase portion of SEQ ID NO:16, a composition comprising said antisense compound and a pharmaceutically acceptable carrier or diluent, a method of inhibiting the expression of groEL or groES in cells or tissues in vitro comprising contacting said cells or tissues with said antisense compound, an antisense oligonucleotide comprising 5 to 50 nucleotides which are complementary to the groEL or groES gene of a microorganism, a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of said antisense

oligonucleotide, a method of inhibiting the expression of a groEL or groES gene in a microorganism comprising administering to said microorganism an effective amount of said antisense oligonucleotide, an antisense oligonucleotide comprising 5 to 50 nucleotides being capable of binding to the groEL or groES gene of a microorganism and comprising all or part of the sequence SEQ ID NO: 16, a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of said antisense oligonucleotide a method of inhibiting the growth of a microorganism comprising identifying said microorganism and administering to said microorganism an effective amount of an antisense oligonucleotide comprising at least 5 nucleotides being complementary to either the groEL or groES gene of said microorganism.

2. Claims : 1-40 partially

Idem as subject 1 but limited to SEQ ID NO: 17.

3 to 465 Claims : 1-40 partially.

Idem as subject 1 but limited to SEQ ID NOs: 18-480 (corresponding to Tabs 1-4 of the description).

The technical feature common to the 465 inventions is that they are related to bacterial groEL or groES genes.

However, antisense oligonucleotides targeted to groEL and groES nucleic acid sequences of several bacterial origins and their use as antimicrobial agents in pharmaceutical compositions already known in the prior art (see WO9803533, page 19, line 1 to page 37, line 9; page 42, line 18 to page 48, line 3; page 51, line 18 to page 57, line 15 and page 82, table 1). Therefore, there is no novel technical feature linking inventions 1-465 in the sense of Rule 13(2) PCT.

In the light of the prior art, the problem underlying the present application can be defined as the provision of further antisense oligonucleotides targeted to groEL and groES nucleic acid sequences of different bacterial origins.

Invention 1-465, corresponding to the antisense oligonucleotides targeted to nucleic acids encoding different bacterial groEL or groES polypeptides as described in tables 1-4, are the different solutions to this problem.

In view of the fact that antisense oligonucleotides targeted to several bacterial groEL and groES nucleic acid sequences and their use as antimicrobial agents are known in the prior art and due to the fact that no other technical features ca be distinguished which, in the light of the prior art, could be regarded as special technical features common to these solutions in the sense of Rule 13.2 PCT, i.e. that there are essential differences in primary structure between these antisense oligonucleotides, the IPEA shares the advice of the ISA that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently, there is a lack of unity.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application refers to antisense compounds (5-50 nucleotides) targeted to a nucleic acid molecule encoding groEL or groES of a microorganism, wherein said antisense compound hybridizes with and inhibits the expression of groES or groEL and their use for inhibiting groEL or groES expression in a microorganism and the growth of said microorganism and to treat a mammalian pathological condition mediated by such a microorganism.

2. **Reference is made to the following documents :**

   D1: WO 98 03533 A (OLIGOS ETC. AND OLIGOS THERAPEUTICS, INC.) 29 January 1998 (1998-01-29)

   D2: IVIC, A. ET AL.: 'Deletion of Escherichia coli groEL is complemented by a Rhizobium leguminosarum groEL homologue at 37 C but not at 43 C' GENE, vol. 194, no. 1, 18 July 1997 (1997-07-18), pages 1-8, cited in the application

3. Novelty; article 33(2) PCT.

3.1 The document D1 refers to the use of nuclease resistant oligonucleotides for treating animals having an infection caused by a pathogenic bacterium (Abstract). D1 also refer to the use of the antisense oligonucleotides for inhibiting the growth of bacteria (p. 16, lines 16-17) and to the use of such antibacterial oligonucleotide in combination with a pharmaceutically acceptable carrier for the treatment of bacterial infections in animals (p. 17, lines 6-11). The antisense oligonucleotides should have a size ranging from 8 to 80 nucleotides (p. 25, lines 20-22) and can include modifications (p. 27, line 15 to p. 28, line 15). Oligonucleotides having base-modified nucleoside units are discussed (p. 41). One of the antisense oligonucleotides used (NBT 66, Table 1, p. 82) is directed to the groESL operon.

Therefore, the subject-matter of claims 1-2, 4-14, 27-28, 30, 32-33, 36-37 and 40 can not be considered as novel as far as said claims refer to a general antisense oligonucleotide directed against a groEL or groES gene (article 33(2) PCT).

3.2 The subject-matter of claims 3, 15-26, 29, 31, 34-35 and 38-39 has never been disclosed in the documents cited in the International Search Report (ISR). Therefore, claims 3, 15-26, 29, 31, 34-35 and 38-39 are considered as novel in the sense of article 33(2) PCT.

4. Inventive step; article 33(3) PCT.

The most relevant document for the evaluation of the inventiveness of the claims is the document D1.

In view of the teaching of D1 (see point 3 for the content), the problem to be solved by the present application is the provision of a further antisense oligonucleotide targeted to a nucleic acid molecule encoding groEL or groES.

The present application solves this problem by the selection of an antisense compound comprising a portion of at least 5 "nucleobases" and up to 50

"nucleobases" of SEQ ID NO:16.
In order to be considered as inventive, the selection of this particular antisense compound should not be arbitrary but motivated by a technical purpose, i.e. a hitherto unknown or unexpected technical effect due to the selection of the specific antisense compound comprising from 5 to 50 "nucleobases" of SEQ ID NO:16 over the antisense oligonucleotide disclosed in D1.

At the moment, no such technical effect can be identified by the IPEA. Therefore, claims 1-40 can not be considered as inventive in the sense of article 33(3) PCT.

The attention of the applicant is also drawn to document D2 :
D2 discloses the fact that the groEL gene is an essential gene (p. 4, right-hand column, third paragraph) and that the depletion of groEL appears to be a bacteriocidal event (p. 5, left-hand column last two lines to right-hand column, first paragraph).
The IPEA considers that the skilled person would have needed no inventive activity to combine the teaching of D1 (generation of antisense oligonucleotides resistant to nucleases and use of said antisense oligonucleotides for inhibiting bacterial growth and for the treatment of infection in animals) and the teaching of D2 (suppression of groEL expression is a bacteriocidal event), thus arriving to the subject-matter of the present application.

5. Industrial applicability; article 33(4) PCT.

Claim 40 of the present application is directed to a method of treatment of the human or animal body.
For the assessment of the present claim 40 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.